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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/667,216 | 09/19/2003 | Shaker A. Mousa | 2747/1021 | 7027 |

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EXAMINER

KHARE, DEVESH

ART UNIT

PAPER NUMBER

1623

| SHORTENED STATUTORY PERIOD OF RESPONSE | MAIL DATE | DELIVERY MODE |
|--|------------|---------------|
| 3 MONTHS | 01/26/2007 | PAPER |

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

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|------------------------------|--------------------------------------|---|--|
| Office Action Summary | Application No. 10/667,216 | Applicant(s) MOUSA, SHAKER A. | |
| | Examiner Devesh Khare | Art Unit 1623 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 02 November 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,2,5,6,43,49-54,56-59 and 61-90 is/are pending in the application.
- 4a) Of the above claim(s) 64-90 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,2,5,6,43,49-54,56-59 and 61-63 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

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A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office Action has been withdrawn pursuant to 37 CFR 1.114.

The amendments and remarks received on 11/02/2006 have been entered. Claims 1-2, 5-6, 43, 49-54 and 56-59 have been amended. New claims 61-90 have been added. Claims 3-4, 7-42, 44-48, 55 and 60 have been cancelled.

The method claims had been withdrawn previously in response to the restriction requirement dated 03/25/2005. Therefore, the newly added method claims 64-90 of the same subject matter have also been withdrawn.

The rejection under 35 U.S.C 112, second paragraph, of the office action dated 03/08/2006 has been overcome in response to the applicant's amendments dated 11/02/2006.

During the course of reconsideration of the application, new prior art not previously disclosed by the applicants or the examiner came to light therefore rejection under 35 U.S.C 103(a) is being presented over new grounds (see rejection below).

The following is new rejection(s) necessitated by Applicant's amendment filed on 11/02/2006.

An action on the merits of claims 1, 2, 5, 6, 43, 49-54, 56-59 and 61-63 is contained herein below.

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35 U.S.C. 103(a) rejection

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1, 2, 5, 6, 43, 49-54, 56-59 and 61-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mascellani et al. (Mascellani) (U.S. Patent 4,973,580) in combination with Weitz et al. (Weitz) (U.S. Patent 6,075,013) in view of Cohen et al. (Cohen) (U.S. Patent 5,908,837) in combination with Scholander (U.S. Patent 6,461,665).

It is noted that in the composition claims 1, 2, 5 and 6, the recitation of an intended use such as the inherent properties of the oxidized heparin fraction, which comprises an anticoagulant reduction characteristic and an angiogenesis inhibition characteristic, is not afforded any patentable weight. Therefore, said inherent properties are not considered the limitation of claims 1, 2, 5 and 6.

Mascellani discloses the depolymerized or oxidized heparins, heparin sulfate, dermatan sulfates and chondroitin sulfates (abstract). Mascellani discloses the oxidizing process of heparin with periodate to produce a reduced molecular weight product and a pharmaceutical composition thereof having a high antithrombotic activity, poor or no anticoagulant activity, a high fibrinolytic activity and an anti-inflammatory activity with a good bioavailability (col. 1, lines 15-25). Mascellani is silent in disclosing the oxidized

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percent range of the oxidized hydroxyl groups by the said process. Mascellani discloses the said heparin with a low molecular weight ranging between 2000-7000 (col. 4, lines 55-60). Mascellani also discloses the sulfate to carboxylate ratio between $>2:1$ (col. 6, Table 1). Mascellani discloses that the oxidation process does not change the sulfate content of heparin, which is important for the biological activity (col. 4, lines 35-40).

Mascellani discloses the good bioavailability of said reduced molecular weight fractions after oral administration (col.1,line 25); although the prior art is silent in disclosing the sustained release of said fraction however it will be obvious to one skilled in this art to use said fraction to accomplish the sustained release of the heparin fraction.

Furthermore, Mascellani discloses the pharmaceutical compositions for parenteral, topical and oral administration (col.4, lines 60-65); the encapsulated forms such as tablet and capsule are disclosed (col.5, line 5. Mascellani differs from the applicant's invention that Mascellani does not provide an explicit example of a composition containing an oxidized heparin fraction, which is super-sulfated in combination with a non-heparin anticoagulant.

Weitz teaches modified low molecular weight oxidized heparin (MLMWH) between 3,000-8000 Daltons (col.10, lines 25-30). Weitz discloses that MLMWH can be obtained by periodate oxidation of heparin (col.10, lines 47-53). Weitz discloses that MLMWH can be incorporated as components in pharmaceutical compositions which are useful either alone or in conjunction with conventional thrombolytic treatments and anti-platelet treatments (col.11, lines 20-30). Weitz also discloses the pharmaceutically active amounts of MLMWH such as at a concentration of 2 μg to 200 μg per dose (col.12, lines

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61-65). Weitz discloses that MLMWH can be prepared from low molecular weight heparin or unfractionated heparin having an average molecular weight between 3,000-8,000 Daltons therefore it would be obvious to one skilled in the art that a composition comprising MLMWH may also comprise standard heparin fraction (col.7, lines 47-52) however MLMWH are considerably better than standard low molecular weight heparin in the inhibition of thrombin generation by catalyzing factor Xa inactivation by antithrombin (col.4, lines 10-22). Weitz discloses a process wherein the unfractionated heparin is depolymerized to yield low molecular weight heparin (col.8, lines 22-26) and further can be detected or isolated using a chromatography process such as gel permeation chromatography, HPLC, ultrafiltration, size exclusion chromatography etc. (col.7, lines 47-63). With regard to an oxidized heparin fraction, which is super-sulfated of claim 1, it would be within the scope of the artisan in this art to isolate a heparin fraction which is rich in sulfate groups through routine chromatography experimentation as taught by Weitz, because sulfated heparin are well known for their thrombolytic activities.

Cohen teaches the use of low molecular weight heparins in a pharmaceutical composition in combination with a non-heparin angiogenesis inhibitor (col.3, lines 50-60). Cohen discloses periodate oxidized heparins having a low molecular weight between 3000-6000, a pharmaceutical composition containing a pharmaceutical carrier (col. 4, lines 10-45). Cohen also discloses that the combination of the heparin and a non-heparin agent is more effective in the inhibition of angiogenesis (col. 3, lines 57-58).

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Therefore applicant's use of a non-heparin anticoagulant or a cytotoxic or chemotherapeutic agent in combination with the low molecular weight oxidized heparin fraction are obvious over the prior art.

With regard to a polymeric structure comprising the oxidized heparin fraction of claims 56-59 and 61-63, Scholander teaches a process for the preparation of modified surface wherein heparin is attached to the surface to accomplish an improved antithrombogenic activity (abstract). Scholander discloses that heparin can be attached to a surface by covalent links via functional groups such as aldehyde, carboxylic acid or amino groups (col.3, lines 32-39). Scholander discloses that the polymeric surface such as polyethyleneimine, chitosan or polysaccharides can be used for modifying with heparin (col.4, lines 40-45). Scholander also discloses the surface modification on medical substrates that do not carry functional groups on their surface (col.4, lines 22-39). Furthermore, Scholander discloses that oxidized heparin when immobilized on a surface can provide a highly enhanced heparin activity (col.7, lines 25-29).

It would have been obvious to person having ordinary skill in the art at the time the invention was made, to select an oxidized heparin fraction or a composition thereof having molecular weight between 2,000-4,000 daltons wherein the oxidized heparin fraction is super-sulfated and/or in combination with a non-heparin anticoagulant; angiogenic inhibitor; or cytotoxic or chemotherapeutic agent and a polymeric structure comprising the oxidized heparin fraction, since Mascellani teaches oxidized heparin with

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a low molecular weight ranging between 2000-7000 and Cohen teaches the use of low molecular weight oxidized heparins in a pharmaceutical composition in combination with a non-heparin angiogenesis inhibitor. Furthermore, Macellani and Weitz teach that low molecular weight oxidized heparin are more active compare to standard low molecular weight heparin for their antirhombotic activities and Scholander teaches that the activity of oxidized heparin can be considerably enhanced by immobilizing them on a polymeric surface. Mascellani provide the motivation to use oxidized low molecular weight heparin fraction and a pharmaceutical composition thereof due to their high antithrombotic activity, poor or no anticoagulant activity, a high fibrinolytic activity and an anti-inflammatory activity with a good bioavailability (sustained release) (col. 1, lines 15-25).

Response to Arguments

Applicants' arguments traversing the rejection of claims 1, 2, 5, 6, 43, 49-54, 56-59 and 61-63 under 35 U.S.C 103(a) have been fully considered but they are not persuasive.

Applicants argue, Mascellini in view of Cohen does not teach or suggest the claimed first anticoagulant reduction characteristic; second anticoagulant reduction characteristic; and angiogenesis inhibition characteristic, of the oxidized heparin.

It is noted that in the composition claims 1, 2, 5 and 6, the recitation of an intended use such as the inherent properties of the oxidized heparin fraction, which comprises an anticoagulant reduction characteristic and an angiogenesis inhibition characteristic, is not afforded any patentable weight. Therefore, said inherent properties are not considered the limitation of claims 1, 2, 5 and 6.

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Mascellani discloses the oxidizing process of heparin with periodate to produce a reduced molecular weight product and a pharmaceutical composition thereof having a high antithrombotic activity, poor or no anticoagulant activity, a high fibrinolytic activity and an anti-inflammatory activity with a good bioavailability (col. 1, lines 15-25).

Weitz discloses that MLMWH can be incorporated as components in pharmaceutical compositions, which are useful either alone, or in conjunction with conventional thrombolytic treatments and anti-platelet treatments (col.11, lines 20-30).

Macellani and Weitz teach that low molecular weight oxidized heparin are more active compare to standard low molecular weight heparin for their antirhombotic activities and Scholander teaches that the activity of oxidized heparin can be considerably enhanced by immobilizing them on a polymeric surface.

The patentability of a product does not depend on its method of production or its use. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process. *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985).

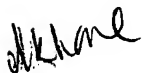
Any inquiry concerning this communication or earlier communications from the

Examiner should be directed to Devesh Khare whose telephone number is (571)272-0653. The examiner can normally be reached on Monday to Friday from 8:00 to 4:30.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anna Jiang, Supervisory Patent Examiner, Art Unit 1623 can be reached at (571)272-0627. The official fax phone numbers for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Devesh Khare, Ph.D., J.D.

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January 22, 2006